

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



## Estrogen and Brain Protection

Xiaohua Ju, Daniel Metzger and Marianna Jung  
*University of North Texas Health Science Center*  
 USA

### 1. Introduction

In 1931, estrogen was originally discovered as a female sex hormone by Marrian and Butenandt (1931). Estrogen is responsible for maintaining female reproductive organs and functions. Beyond the effects on reproductive organs, the neuroprotective activities of estrogen have been identified by Simpkins et al. (1994) and thereafter by numerous other researchers (Viscoli et al., 2001). The simple classification of the mechanisms of estrogen is genomic and non-genomic processes. The genomic mechanisms of estrogen involve estrogen receptors located in DNA. Upon binding its receptors, estrogen stimulates the synthesis of a variety of neuro-modulatory proteins. A body of evidence indicates that estrogen receptors are not necessary for certain neuroprotective effects of estrogen. For example, estrogen scavenges harmful reactive free radical species (Dhandapani & Brann, 2002), inhibits apoptotic process (a certain type of cell death), and modulates signal transduction, all of which do not require nucleic estrogen receptors. Estrogen's neuroprotective properties may be the end result of well-orchestrated genomic and non-genomic processes.

There are three major forms of endogenous estrogens; 17 $\beta$ -estradiol, estrone, and estriol based on the hydroxyl or ketone ligand attached to the C17 position of the rightmost ring (D ring). Among these estrogens, 17 $\beta$ -estradiol (Figure 1) is the most potent, naturally occurring estrogen. Accordingly, 17 $\beta$ -estradiol has been the subject for neuroprotective properties in major neurodegenerative disorders such as stroke, Alzheimer's disease, Parkinson's disease, and ethanol withdrawal, and thus a topic of this book chapter.

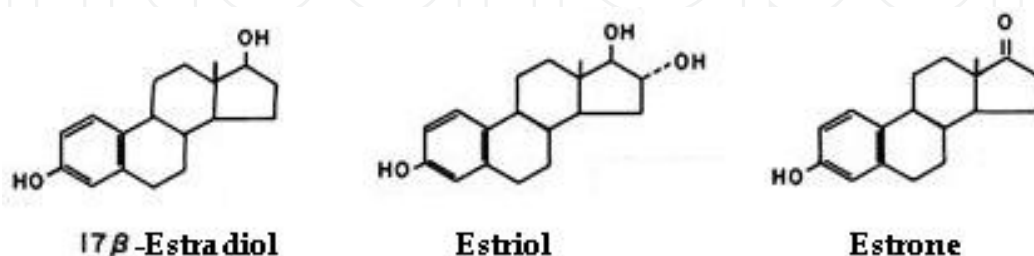


Fig. 1. Chemical structures of 17 $\beta$ -estradiol, estriol, and estrone. Notice that 17 $\beta$ -estradiol has two hydroxyl (OH) groups, estriol has three hydroxyl groups, and estrone has one hydroxyl and one ketone group.

## 2. Estrogen and ischemia

### 2.1 Introduction

Stroke is the sudden loss of brain function that is attributed to ischemia which indicates a disturbance in the blood supply to the brain. The affected brain area is unable to function, resulting in an inability to move limbs, understand or formulate speech, or an inability to see the visual field. It is the leading cause of adult disability in the United States and Europe and the second leading cause of death worldwide (Feigin, 2005). Women have a higher risk, due to their longer lifespan and are also more likely to have fatal strokes than men (Bushnell, 2008). Especially women in the 45–54 age range (perimenopause) are reportedly at a higher risk for stroke (Towfighi et al., 2007). This study suggests that declining levels of ovarian hormones perpetuate the risk for this neurovascular disease. The depletion of ovarian hormones also alters stroke outcomes. In postmenopausal women, stroke-associated disability and fatality are worse compared to men (Niewada et al., 2005). If ovarian hormones influence stroke, it is not surprising to see sex differences in the severity of stroke. For instance, a smaller area of tissue death was found in young adult female mice (Park et al., 2006) compared to their age-matched males. Furthermore, the sex difference in stroke infarct (area of tissue death) was abolished when the female mice were ovariectomized, suggesting that ovarian steroids mediate the neuroprotection seen in younger females (Selvamani et al., 2010).

Among ovarian hormones,  $17\beta$ -estradiol seems to possess greater protective properties than other ovarian hormones.  $17\beta$ -estradiol mitigated brain inflammation (Suzuki et al., 2009) and blood-brain barrier dysfunction (R. Liu et al., 2005).  $17\beta$ -estradiol increased the blood flow of the cerebrum (Pelligrino et al., 1998), the ability of neurons to transmit signals (synaptic plasticity), and cognitive function (Sherwin, 2007). By comparison to these protections in animal studies, human studies showed somewhat inconsistent results. In large clinical trials, such as the Women Estrogen Stroke Trial and the Women's Health Initiative, estrogen treatment failed to exert the beneficial effects on stroke incidence (Viscoli et al., 2001). Rather, the clinical study showed that estrogen treatment increased the stroke risk and worsened neurological outcomes in postmenopausal women (Viscoli et al., 2001). Similarly, the Women's Health Initiative study reported an increased risk for stroke following the treatment with estrogen or another female hormone progestin (synthetic progesterone) (Wassertheil-Smoller et al., 2003). Notably, many women in these clinical trials were postmenopausal for several years prior to the hormone treatment. The unexpected negative results might have been due to prolonged estrogen-withdrawal before estrogen was reintroduced (De et al., 2009). Other researchers suggested that differences in the duration of treatment, timing of administration, sex, age, and an ischemia model contributed to the inconsistent outcome of estrogen therapy (J. Li, 2011; Sherwin, 2009).

### 2.2 Apoptosis

Apoptosis is a type of cell death that normally occurs to replace aged or injured cells with newer cells. However, excessive or defective apoptosis is often present at regions affected by stroke (Dirnagl et al., 1999). Fas is a receptor protein that triggers apoptotic cell death upon the binding of its ligand (Fas ligand). The structure of Fas contains a particular region, called 'death domain'. There is a cytoplasmic protein that favors to associate with the death domain of Fas. Therefore, it is called Fas-associated death domain adaptor protein. When this adaptor protein binds to the death domain of Fas, it subsequently activates

another apoptotic protein, caspase-8. An increasing body of work has shown that Fas and Fas Ligand play an important role in the pathology of ischemic stroke (L. Liu et al., 2008; Rosenbaum et al., 2000). Both Fas and Fas ligand were upregulated by cerebral ischemia in brains of developing, as well as adult mice (Felderhoff-Mueser et al., 2000, 2003). Intriguingly, estrogen significantly reduced the level of Fas and the adaptor protein in mice undergoing post-ischemic stress (Jia et al., 2009). Furthermore, estrogen reduced the downstream apoptotic effectors such as caspase-8 and caspase-3. These findings suggest that estrogen protects against ischemia, in part, through its inhibitory effects on apoptosis associated with Fas (Jia et al., 2009).

Estrogen also protects neurons from ischemia (Petito et al., 1987). Estrogen administered at physiological levels for two weeks before ischemia rescued the hippocampal neurons and ameliorated ischemia-induced cognitive deficits in female rats (Lebesgue, 2009). This study provides direct evidence that estrogen is neuroprotective against ischemia. There are at least two estrogen receptors in the brain, estrogen receptor- $\alpha$  and - $\beta$  (Shughrue, 2004). Estrogen receptors are intracellular proteins which activate genomic as well as nongenomic effectors in neural cells (Maggi et al., 2004). Selective agonists for estrogen receptor- $\alpha$  or estrogen receptor- $\beta$  were able to spare hippocampal neurons following ischemia. In addition, ICI 182780, a competitive antagonist for both estrogen receptors- $\alpha$  and - $\beta$ , completely blocked estrogen's protection against post-ischemic stress (Miller et al., 2005). On the other hand, Lebesgue et al. (2009) found that a single injection of estrogen into the brain ventricle immediately after an ischemic event reduced both neuronal death and cognitive deficits. The genomic mechanism of estrogen is typically a slow process because it involves estrogen's receptors in the nuclei, affecting protein synthesis. Therefore, the rapid protection achieved by acute estrogen in Lebesgue's study may indicate the non-genomic effects of estrogen.

Above studies suggest that estrogen exerts neuroprotection against ischemia through its anti-apoptotic property and the mechanisms associated with estrogen receptors.

### 2.3 Oxidative stress

When ischemic patients receive blood supply (reperfusion), the introducing blood itself can induce significant damage to the brain. The damage is largely attributable to very active harmful oxygen species such as the reactive superoxide anion (Peters et al., 1998; Sugawara et al., 2005). These oxygen species give rise to other damaging oxygen species, for example, hydroxyl ion and peroxynitrite (Mattson et al., 2000). Estrogen contains profound antioxidant properties that mediate its protective effects on neurons. Estrogen directly scavenges free radicals by oxidizing its hydroxyl group attached to the C3 position of A ring (left most ring) through an enzyme, NADPH. The A ring then becomes the phenoxyl radical ring, a certain type of a ring structure containing free radicals. The phenoxyl radical ring is converted to para-quinol ring by scavenging further free radicals like -OH. This para-quinol ring structure finally becomes the original A ring of 17 $\beta$ -estradiol through NADPH (Prokai et al., 2003; Prokai-Tatrai et al., 2008). The important point of this cyclic reaction is that 17 $\beta$ -estradiol is rejuvenated after it absorbs harmful free radicals (Figure 2). Indeed, estrogen attenuated superoxide production in hippocampal neurons after stroke (Q.G. Zhang et al., 2009). In addition to this directly scavenging of free radicals, estrogen upregulates antioxidant enzymes and chelates redox-active metal ions. In terms of estrogen receptor, Zhang et al. (2009) suggested that the antioxidant effect of estrogen is independent of estrogen receptor- $\alpha$ . They found that estrogen deprivation abolished the antioxidant and

neuroprotective effects on the hippocampus without affecting estrogen receptor- $\alpha$  mediated effect on the uterus. At the very least, these findings indicate that estrogen protects against ischemia through antioxidant properties.

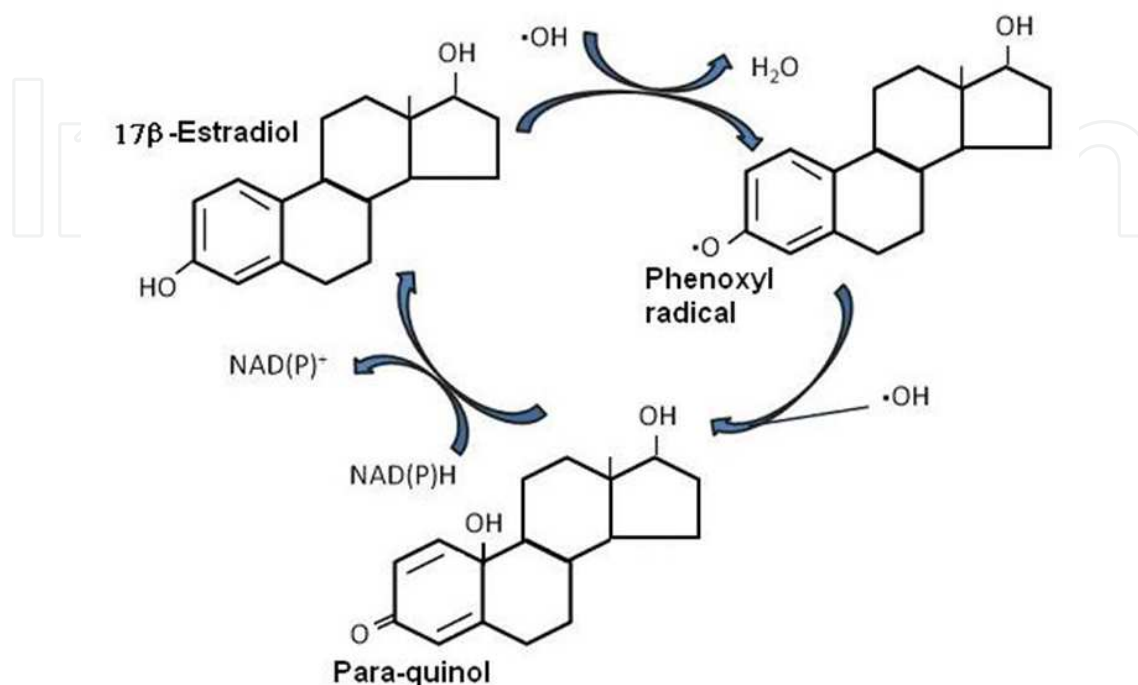


Fig. 2. Schematic illustration of the free radical scavenging antioxidant activity of 17 $\beta$ -estradiol. 17 $\beta$ -estradiol captures  $\cdot\text{OH}$ , producing the phenoxyl radical and then bioreversible quinol. The quinol is rapidly converted to the parent estrogen via a NAD(P)H-dependent reductive aromatization to perpetuate the antioxidant action. During this process,  $\cdot\text{OH}$  is detoxified to  $\text{H}_2\text{O}$  (Prokai et al., 2003; Prokai-Tatrai et al., 2008).

## 2.4 Inflammation\Immune response

Inflammation is a critical event that occurs upon ischemic insults. Post-stroke events include the stimulation and subsequent degeneration of lymphoid organs such as the spleen and thymus (Offner et al., 2009). The activation of these lymphoid organs likely leads to immunocyte translocation into brain, exacerbating the evolving brain ischemia (Ajmo et al., 2008). Proinflammatory genes are rapidly induced in brain after ischemic injury, including genes synthesizing TNF- $\alpha$  (X. Wang et al., 1994), IL-6 (X. Wang et al., 1995), IL-1 $\beta$  (X. Wang et al., 1994), and interferon inducible protein-10 (IP-10) (X. Wang et al., 1998). The subsequent degeneration of lymphoid organs leads to immunodepression. Humans who survive the initial brain insult, may succumb to fatal infection due to the immunodepression (Dirnagl et al., 2007; Meisel et al., 2005).

Estrogen deficiency during menopause is associated with a proinflammatory phenotype, namely 'T cell expansion' in bone marrow that secretes inflammatory proteins such as IL-1, TNF- $\alpha$ , and IL-6 (Pfeilschifter et al., 2002). In a study done by Zhang et al. (2010), estrogen partially restored immune reactivity in ovariectomized females by increasing spleen cell population and cytokine responses (B. Zhang et al., 2010). In agreement, estrogen induced anti-inflammatory cytokines in the spleen after traumatic brain injury (Bruce-Keller et al.,



2007). In lipopolysaccharide-induced brain inflammation, estrogen suppressed both resident microglial activation and the recruitment of peripheral T and B cells (Vegeto et al., 2001). These studies provide empirical evidence that the anti-inflammatory effect of estrogen plays a protective role in immune responses to stroke.

Collectively, cumulative evidence indicates that the convergence of endocrine changes, especially estrogen, impacts the pathophysiology of stroke and ischemic injury. It appears that estrogen protects against ischemia through multiple factors associated with apoptosis, inflammation, redox, and estrogen receptors. Understanding these mechanisms may ultimately contribute to better research and therapeutic strategies for stroke therapy.

### 3. Estrogen and Alzheimer's disease

#### 3.1 Introduction

Alzheimer's disease is characterized as a gradual failure of memory, cognition, and bodily functions, ultimately leading to death. Although the exact etiology and mechanisms are unknown, the abnormal accumulation of a particular protein, called Amyloid  $\beta$ , has long been proposed as the most likely culprit in the pathogenesis of this disease (Hardy & Selkoe, 2002; Tanzi & Bertram, 2005). In a healthy brain, Amyloid  $\beta$  remains at a steady-state level as a result of the metabolic balance between production of Amyloid  $\beta$  from amyloid precursor protein and removal by cellular uptake and proteolytic degradation (Saido, 1998; Selkoe, 2000). Such a dynamic equilibrium, however, could be altered by genetic or environmental factors that may lead to Alzheimer's disease. It has been hypothesized that Amyloid  $\beta$  is folded into a oligomeric form or a fibrillar (cable-like strings) form (Yamin et al., 2008), both of which are more neurotoxic than Amyloid  $\beta$  itself. Of several different Amyloid  $\beta$  peptides produced, products of Amyloid  $\beta$ -40 and Amyloid  $\beta$ -42 residues are the most common constituents of amyloid plaques, and are widely accepted as the primary trigger for Alzheimer's disease (St George-Hyslop, 2000). In brains with early onset Alzheimer's disease, Amyloid  $\beta$  excessively accumulates. This may be due to the mutations of presenilin genes, which provoke the overproduction of Amyloid  $\beta$  from amyloid precursor protein (Hardy, 2004). In late-onset Alzheimer's disease, which constitutes more than 90% of the disease, the excess accumulation of Amyloid  $\beta$  has been associated with abnormal Amyloid  $\beta$  degrading proteases (Nalivaeva et al., 2008).

Women are more likely to develop Alzheimer's disease after adjusting for age (Andersen et al., 1999). After menopause, the decline of estrogen levels in the brain may render neurons more susceptible to age-related neurodegenerative processes (Coffey et al., 1998). Estrogen therapy, when initiated at the onset of menopause, has reduced the risk or delayed the onset of Alzheimer's disease in women (LeBlanc et al., 2001; Zandi et al., 2002). A recent randomized control trial indicated that estrogen treatment had a beneficial effect on verbal memory in men with mild cognitive impairment (Sherwin et al., 2011 in press). However, clinical studies of estrogen therapy in non-demented and menopausal women have yielded inconclusive results (Craig & Murphy, 2010; Sano et al., 2008). In addition, estrogen administration induced beneficial effects on neuronal function and survival through improving mitochondrial function in healthy neurons (Brinton, 2008). When neurons became unhealthy, estrogen exposure had a detrimental effect (Brinton, 2008). This discrepancy may be due to differences in neurological health, age, hormonal status, the severity of symptoms, the type of menopause (surgical vs. natural), and the type of estrogen compound used (Brinton, 2009). Also, the age when estrogen therapy is initiated, may in part determine the

outcome of estrogen therapy and probably estrogen treatment during the peri-menopause has the highest efficacy (Craig & Murphy, 2010; Genazzani et al., 2007).

In diverse animal models of Alzheimer's disease, estrogen has prevented or delayed the development of Alzheimer's disease pathology in particular Amyloid  $\beta$  accumulation and plaque formation (Carroll et al., 2007; Zheng et al., 2002). Mechanistically, estrogen may regulate the production of Amyloid  $\beta$  and in turn, sustain an improved Amyloid  $\beta$  homeostasis by increasing the metabolism of amyloid precursor protein and destabilization of Amyloid  $\beta$  fibrils (Greenfield et al., 2002; Morinaga et al., 2007). Estrogen's bioenergetic protection may also influence Alzheimer's disease. For instance, estrogen prevented the brain from using alternative fuel sources, such as the ketones (Brinton, 2008, 2009). Aromatase catalyzes the conversion of testosterone to estrogen. Not surprisingly, mice lacking aromatase genes (low estrogen production) showed the loss of hippocampal neurons in response to neurotoxins more severely than wild type mice (Azcoitia et al., 2001), suggesting that estrogen spared those neurons. Indeed, the levels of estrogen and aromatase were significantly reduced in the brains of Alzheimer's disease women (Yue et al., 2005). The view of brain estrogen deficiency as a risk factor for developing Alzheimer's disease pathology is consistent with genetic studies showing an association between the aberration of aromatase gene and the risk for Alzheimer's disease (Iivonen et al., 2004). All these studies suggest that estrogen may have the capacity to interfere with the pathways mediating Alzheimer's disease.

### 3.2 Estrogen synthesis in Alzheimer's disease

Since estrogen has a potential capacity to control Alzheimer's disease, one therapeutic strategy might be to target the biosynthesis of estrogen. Indeed, numerous studies have tested whether Alzheimer's disease alters the endogenous synthesis of estrogen. While the levels of estrogens were unchanged in the prefrontal cortex of Alzheimer's disease patients (Rosario et al., 2011), the estrogen biosynthetic enzymes such as aromatase and 17 $\beta$ -hydroxysteroid dehydrogenase type 1 were upregulated in the late stages of Alzheimer's disease (Luchetti et al., 2011). Studies using immunohistochemistry showed that aromatase expression was upregulated in astrocytes in later stages of Alzheimer's disease (Azcoitia et al., 2003). Another immunochemistry study also detected an increase in the level of aromatase in the hypothalamic neurons of Alzheimer's patients (Ishunina et al., 2005). The increase was especially profound in the Nucleus basalis of Meynert, a nucleus that is strongly affected in Alzheimer's disease (Ishunina et al., 2005). These findings suggest that during Alzheimer's disease, there is an attempt to increase the biosynthesis of estrogen. The aromatase upregulation may be a defense mechanism of brain areas that undergo neurodegeneration. In support of this notion, the reduced levels of testosterone were found in the aging brain of male and female Alzheimer's patients (Rosario et al., 2011; Weill-Engerer et al., 2002). This seems in line with the idea of a compensatory mechanism, since testosterone is used up after it is locally metabolized into neuroprotective estrogen.

### 3.3 Amyloid $\beta$

Cumulative evidence indicates that estrogen protects against Amyloid  $\beta$  and its toxicity through mechanisms involving Amyloid  $\beta$  degradation and signaling changes. Estrogen deficiency accelerated the formation of Amyloid  $\beta$  plaque in mice (Yue et al., 2005). Estrogen treatment reduced the level of Amyloid  $\beta$  (Jaffe et al., 1994; Xu et al., 1998) and its

availability through enhancing the uptake of Amyloid  $\beta$  by microglia (R. Li et al., 2000). In vitro estrogen treatment inhibited the formation of toxic Amyloid  $\beta$  oligomers (Morinaga et al., 2007). Finally, estrogen activated Neprilysin, the primary enzyme that degrades Amyloid  $\beta$ , thereby facilitating Amyloid  $\beta$  degradation in human neuroblastoma cells (Liang et al., 2010). It is possible that this effect of estrogen is preceded by estrogen's action on amyloid precursor protein. Several studies support this notion that estrogen treatment profoundly decreased the levels of amyloid precursor protein by enhancing the degradation of this precursor through the  $\alpha$ - and  $\beta$ -secretase pathways (Amtul et al., 2010). Alternatively, estrogen may reduce available amyloid precursor protein by stimulating the formation of vesicles that uptake this precursor-protein, thereby precluding maximal generation of Amyloid  $\beta$  (Greenfield et al., 2002). These findings suggest another mechanism underlying estrogen's protection against Alzheimer's disease involving Amyloid  $\beta$  degradation (Liang et al., 2010). Estrogen may also protect the signaling function of protein kinases from Amyloid  $\beta$ . For example, Amyloid  $\beta$  oligomer inhibited the activity of calcium/calmodulin-dependent protein kinase II and extracellular signal-regulated kinase in a manner ameliorated by estrogen treatment (Logan et al., 2011). In agreement with the protective effect of estrogen on protein kinase, Szego et al. (2011) reported that the function of protein kinases correlated with avoidance learning behavior. In that study, the treatment with Amyloid  $\beta$  oligomers impeded the learning in a manner that was protected by estrogen. These studies suggest a diverse mechanism by which estrogen protects against Amyloid  $\beta$  as an attempt to cope with Alzheimer's disease.

### 3.4 Neuroinflammation

The neurotoxicity of Alzheimer's disease is in part mediated by inflammatory processes (McGeer et al., 2006). Glial cells (non neuronal cells) are involved in this process such that Amyloid  $\beta$  activates glial cells to produce pro-inflammatory cytokines like IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Activated glial cells have the potential to produce large amounts of reactive oxygen species/nitrogen species by various mechanisms (Zhu et al., 2007). Activated astrocytes produced excessive nitric oxide, which reacted with superoxide to form harmful peroxynitrite (Smith et al., 1997). Excess nitric oxide synthetase was also detected in astrocytes surrounding plaques in Alzheimer's disease (Luth et al., 2001). Estrogen interfered with this process by limiting astroglial cells and inhibiting chronic inflammation associated with Alzheimer's disease (Vegeto et al., 2003). The anti-inflammatory effects of estrogen were shown in a primary culture study; estrogen treatment decreased the expression of pro-inflammatory molecules, such as TNF- $\alpha$  and IL-1 $\beta$ , as well as nitric oxide synthase and cyclooxygenase-2 in astrocytes (Valles et al., 2010).

Vegeto et al. (2006) conducted a study further supporting the protective effects of estrogen on inflammation associated with Alzheimer's disease. They used the APP23 mouse model, a model of Alzheimer's disease that creates chronic neuroinflammation resembling that in Alzheimer's disease. They found that the number of plaques associated with reactive microglia was increased with age (Vegeto et al., 2006). Interestingly, ovariectomy accelerated microglial activation surrounding Amyloid  $\beta$  plaques, whereas estrogen replacement delayed this process. In parallel, they showed that estrogen reduced the expression of inflammatory mediators, such as monocyte chemoattractant protein-1, macrophage inflammatory protein-2, and TNF- $\alpha$ . That study indicates that microglia is a direct target of estrogen action in the brain. All of these findings reinforce the hypothesis



that inflammatory mechanisms significantly contribute to the pathogenesis of Alzheimer's disease and support the use of estrogen in the fight against Alzheimer's disease.

Collectively, animal studies on Alzheimer's disease have shown beneficial effects of estrogen through inhibiting the synthesis of amyloid  $\beta$ , facilitating its metabolisms, modulating protein kinases, and inhibiting inflammatory pathways. Human studies on the effects of estrogen on Alzheimer's disease have resulted in both positive and negative effects. It is unclear what causes the inconsistent results. Nevertheless, it seems clear that estrogen influences Alzheimer's disease pathology, if not etiology. How to identify and adjust factors underlying the discrepancies seems to be an essential task.

## **4. Estrogen and Parkinson's disease**

### **4.1 Introduction**

Parkinson's disease is the second most common neurodegenerative movement disorder. It is mainly characterized by the slow and gradual emergence of motor disorders such as tremor, rigidity, bradykinesia, and postural instability (Lang, 2007). Parkinson's disease is less prevalent in women than in men by an approximate 2:3 ratio and evidence suggests that estrogen influences the onset and severity of disease-associated symptoms (Currie, 2004; Shulman, 2006). Women with Parkinson's disease tend to have an earlier menopause, are more likely to have undergone hysterectomy, and used estrogen therapy less frequently than control subjects (Benedetti et al., 2001). Ragonese et al. (2004) suggested that factors reducing estrogen contribute to the development of Parkinson's disease (Ragonese et al., 2004). This was recently supported by the Observational Study of the Women's Health Initiative (WHI-OS) that employed 83,482 women. The study showed association between the number of women with longer fertile lifespan and a reduced risk of Parkinson's disease (Saunders-Pullman et al., 2009). In another human study, women with Parkinson's disease were less likely to have used postmenopausal estrogen therapy (Currie et al., 2004), suggesting that estrogen produces a beneficial effect on Parkinson's disease.

### **4.2 Dopamine neurotransmission**

Dopamine is a neurotransmitter that has multiple functions in the brain such as cognition, reward, mood, and voluntary movement. The substantia nigra is a brain area that governs these functions. So far, this neurotransmitter has been the major player in Parkinson's disease such that dopamine synthesizing neurons are progressively depleted in the substantia nigra of Parkinson's patients (Emborg, 2004). Aberrant dopamine transmission is implicated in Parkinson's disease, particularly because the symptoms are ameliorated by a drug which increases dopamine signaling. Dopamine is actively eliminated from the extracellular space by astrocytes and neurons through dopamine transporters. Afterwards, dopamine is either recycled into vesicles or metabolized. In previous studies, estrogen increased the availability of dopamine by inhibiting uptake and by decreasing the affinity of the transporter for dopamine (Disshon et al., 1998). Estrogen also increases the synthesis of dopamine in the substantia nigra and the release of dopamine from axon terminals. In rodents and in neuronal cell culture studies, estrogen protected dopaminergic neurons from injury (B. Liu & Dluzen, 2006; Arvin et al., 2000). Given this, the beneficial effect of estrogen on Parkinson's disease may be mediated through estrogen's action on dopamine.

Studies have further identified how estrogen acts on the dopamine system. Estrogen modulates the development of dopaminergic neurons and neurotransmission (Bourque,

2009) by promoting neurite plasticity (Beyer et al., 2000). These effects are either mediated through a direct action on dopaminergic neurons or interactions with local astroglia (Ivanova et al., 2001, 2002). Alternatively, estrogen may act on genetic levels to modulate dopamine. For instance, estrogen regulates dopamine gene expression by activating transcriptional factors (DonCarlos et al., 2009). Estrogen also exerts non-genomic membrane effects, interaction with neurotransmitter receptors, and ionic channel regulation (Garcia-Segura et al., 2009). These studies suggest that estrogen protects against Parkinson's disease through genomic and non-genomic effects on the dopamine system.

Dopamine transporters mediate the uptake of dopamine from synapses to presynaptic vesicles, thereby restoring depleted vesicular dopamine levels (Jourdain et al., 2005). Estrogen stimulated dopamine uptake by nerve cells through neuronal dopamine transporter (D'Astous et al., 2004). On the other hand, estrogen decreased astroglial dopamine uptake, increasing the available levels of synaptic dopamine. This allowed more synaptic dopamine to be taken up by neurons. These studies suggest a few important points: first, not only dopamine neurons but also nigrostriatal astroglia contribute to the metabolic processes of dopamine (Karakaya et al., 2007); second, astroglia are implicated in estrogen-transmitted neuroprotection during dopamine neuro-degeneration (Morale et al., 2006), and finally, as the complementary action of estrogen on neurons, astrocyte and microglia may represent a potential pharmacological target for Parkinson's disease management (Vegeto et al., 2008).

#### 4.3 Oxidative stress

In the process of dopamine being catalyzed by monoamine oxidase, a large amount of reactive oxygen species is produced, resulting in cell death (Hastings et al., 1996; Luo et al., 1998). In addition, dopamine aldehyde generated in the oxidative deamination reaction is 1000-fold more toxic than dopamine (Burke, 2003). Dopamine neurons in Parkinson's disease become vulnerable to oxidative stress (Dexter et al., 1989; Sian et al., 1994) perhaps due to lower levels of glutathione (endogenous antioxidant) than other cell types.

The brain has a predominant defense mechanism against superoxide radicals through antioxidant enzymes such as superoxide dismutase. Studies have demonstrated that superoxide dismutase is implicated in dopamine and Parkinson's disease. Mutant mice that over-expressed or lacked superoxide dismutase were more resistant to (Przedborski et al., 1992) or vulnerable to (Andreassen et al., 2001; J. Zhang et al., 2000) dopamine neurotoxin than wild type mice, respectively. The expression of superoxide dismutase was upregulated in the substantia nigra following the dopamine neurotoxin insult, yet the loss of dopaminergic neurons still occurred (Tripanichkul et al., 2007). These results suggest that there is an attempt to combat the oxidative stress in nigral neurons but not sufficient to spare neurons. The implication of superoxide dismutase in the antioxidant effect of estrogen has been shown in a study done by Tripanichkul et al. (2007). In that study, estrogen treatment increased the expression of superoxide dismutase in the substantia nigra of animals that were treated with the dopamine neurotoxin. This study suggests that estrogen up-regulates superoxide dismutase in critical brain areas, thereby exerting protection against dopamine neurotoxin or Parkinson's disease.

#### 4.4 Neuroinflammation

Neuroinflammation and microglial activation are often seen in Parkinson's disease (McGeer et al., 1988; Hunot et al., 2003) and anti-inflammatory drugs reduce the risk of this disease

(H. Chen et al., 2003; Wahner et al., 2007). A positive correlation was found between antecedent brain injuries, such as trauma or exposure to infectious agents and the development of Parkinson's disease (B. Liu et al., 2003). This correlation implies that the brain inflammatory response to these noxious events, and specifically microglial activation, plays a critical role in Parkinson's disease. In support of this view, researchers have detected pro-inflammatory molecules (e.g. TNF- $\alpha$ ) and excessive reactive oxygen species in the nervous system of Parkinson's disease patients (Hunot et al., 1996; Knott et al., 2000). The inflammatory molecules seem to amplify neuroinflammation as well as neuro-toxicity, ultimately leading to a slow and irreversible destruction of dopaminergic neurons. Using estrogen receptor-null mice, several studies have demonstrated that estrogen receptor- $\alpha$  is involved in the anti-inflammatory activity of estrogen (Dubal et al., 2001; Vegeto et al., 2003). Although estrogen receptor- $\beta$  is expressed widely in brain, it does not seem to mediate the protective effect of estrogen. Or the effects of estrogen receptors on inflammation depend on the brain area (Harris et al., 2003). Whether or which receptor mediates estrogen's protection against inflammatory response still remains unclear.

Collectively, the protective effects of estrogen on Parkinson's disease appear to involve dopaminergic neuroprotection, anti-oxidant activities, anti-inflammatory activities, and estrogen receptors. Considering that Parkinson's disease is more prevalent in male than female patients, how these effects of estrogen can be implemented to clinical usages is an open question. At the very least, estrogen can be used as an interventional tool for a new mechanistic insight into this neurodegenerative disease.

## 5. Estrogen and ethanol withdrawal

### 5.1 Introduction

The distress of alcohol (ethanol) withdrawal is initiated by abruptly removing the inhibitory stimulus of ethanol and thus, is associated with rebound hyper-excitatory stimuli. In general, the overt initial signs of ethanol withdrawal include anxiety, ataxia, muscle incoordination, seizures, coma, and even death (American Psychiatric Association, 2000). While repeating unsuccessful attempts to quit heavy drinking, the brain undergoes random exposure to ethanol and withdrawal, damaging cellular and neuronal integrity (Wober et al., 1998).

The neuronal activity of the brain tends to be hyper-excitabile during ethanol withdrawal due to an increase in the level of glutamate, a major excitatory neurotransmitter (Rossetti & Carboni, 1995). This can result in neuronal damage to vulnerable brain areas such as the cortex, hippocampus, and cerebellum. In addition to this well known glutamate neurotransmission, ethanol withdrawal perturbs the homeostasis of redox balance and signaling mechanisms. For instance, ethanol withdrawal provokes the intense generation of reactive oxygen species and activates stress-responding protein kinases (Jung et al., 2009). In addition, ethanol withdrawal inflicts mitochondrial membranes/membrane potential and suppresses mitochondrial enzymes such as cytochrome c oxidase, all of which impair fundamental functions of mitochondria (Jung et al., 2007, 2009). In our recent study, brain aging occurred earlier in ethanol withdrawn animals than in control-diet animals (Jung et al., 2010). These studies indicate that mal-managed ethanol withdrawal can clearly provoke neurodegenerative disorders.

## 5.2 Oxidative stress

Chronic ethanol consumption and ethanol withdrawal both generate oxidative free radicals and subsequent lipid peroxidation (Nordmann et al., 1990; Montoliu et al., 1994). Lipid peroxidation reflects the interaction between oxygen and the polyunsaturated fatty acids of membrane lipids, generating deteriorating breakdown products. Since the brain consists of a high content of unsaturated membrane lipids, it is a preferred target of both reactive oxygen species and ethanol (Hernandez-Munoz et al., 2000). Ethanol withdrawal-induced oxidative stress was associated with an increase in glutamatergic neurotransmission (Rossetti & Carboni, 1995), the upregulation of calcium channels, and the accumulation of intracellular calcium (Rewal et al., 2005). The functional consequence of prooxidant ethanol withdrawal is shown in several animal and human studies. For instance, enhanced reactive oxygen species concurred with ethanol withdrawal-induced seizure activity in rats (Vallett et al., 1997). The cerebrospinal fluid of patients who underwent ethanol withdrawal showed higher concentrations of excitatory neurotransmitters and oxidative markers (Marotta et al., 1997; Tsai et al., 1998) than control subjects. Higher levels of lipid peroxide and lower levels of superoxide dismutase (antioxidant enzyme) activity were also seen in those patients (Tsai et al., 1998). These studies indicate that the redox imbalance has a causative relationship with ethanol withdrawal insults.

If ethanol withdrawal is a prooxidant stimulus, estrogen treatment should be able to mitigate the stress through its antioxidant property. Our recent findings essentially confirmed the hypothesis using the *in vivo* and *in vitro* model of ethanol withdrawal. Estrogen treatment mitigated reactive oxygen species generation, lipid peroxidation, and protein oxidation (Jung et al. 2004, 2006). Estrogen protection against the prooxidant effect of ethanol withdrawal may involve glutamate transmission because glutamate-induced oxidative stress is attenuated by estrogen (Behl & Manthey, 2000) and the quinol derived from estrogen (Prokai et al., 2003). It is also possible that estrogen elevates the levels of endogenous antioxidants, such as glutathione, so that a favorable redox potential for an antioxidant environment is created (Prokai et al., 2003). Since oxidative molecules are generated mainly from mitochondria, these studies suggest that the antioxidant protection of estrogen against ethanol withdrawal is linked to the mitoprotective activity of estrogen.

## 5.3 Mitochondria

Indeed, the mitoprotective effects of estrogen are interactive with the antioxidant effect by virtue of the fact that mitochondria are the major source and target of oxidative free radicals. The mitoprotective effect of estrogen has been extended to the ethanol withdrawal model in our recent study in which ethanol withdrawal provokes the oxidation of mitochondrial proteins in rats, in a manner mitigated by estrogen. Since cellular energy ATP is mainly generated in mitochondria, it is not surprising that estrogen protects against mitochondrial respiratory deficit during ethanol withdrawal (Jung et al., 2011). Presumably, estrogen plays a role in alleviating the oxidative burden in mitochondria, thus increasing mitochondrial respiration efficiency (J.Q. Chen & Yager 2004; Jung et al., 2011).

## 5.4 Signaling pathways

P38 is referred to as a stress-activated protein kinase because it is often activated in response to a variety of stress. A transient, moderate activation of P38 normally occurs in association



with cell survival or differentiation. However, excess activation generally correlates with pathological conditions (Barca et al., 2008). P38 is activated upon phosphorylation (Moriguchi et al., 1996) and thus, pP38 is often measured as an indicator of P38 activation. A previous study reported that the P38 inhibitor SB203580 attenuated ethanol-induced cell death (Ku et al., 2007), suggesting that P38 activation mediates cytotoxic ethanol. Acute ethanol treatment led to P38 activation (Norkina et al., 2007) and augmented endotoxin-induced pP38 levels in a manner attenuated by P38 inhibitor in human monocytes (Drechsler et al., 2006). Recently, we have demonstrated that estrogen protected against ethanol withdrawal-induced hyperactivation of P38, suggesting that there is a crucial link between estrogen, P38, and ethanol withdrawal (Jung et al., 2010). In that study, middle-age female rats (12-15 month old) were more vulnerable to the ethanol withdrawal-induced P38 activation than young or older rats (Jung et al., 2010). Importantly, chronic estrogen treatment abolished the age difference in P38 activation. These studies indicate that ethanol withdrawal interferes with signaling pathways, including P38, in a manner that depends on age and that is protected by estrogen.

In conclusion, findings from our and others' laboratories suggest that ethanol withdrawal distress is more than a neurotransmitter disorder. It is attributed to the perturbation of redox balance, protein kinase signaling, and mitochondria, all of which can be mitigated by estrogen treatment. Understanding the interaction between ethanol withdrawal and estrogen may contribute to the improvement of the pharmacological treatment of ethanol withdrawal.

## 6. Conclusion

There are some lingering controversies in the neuroprotective effects and underlying mechanisms of estrogen. Nevertheless, numerous studies indicate the profound neuroprotective effects of 17 $\beta$ -estradiol on neurodegenerative diseases including ischemia, Alzheimer's disease, Parkinson's disease, and ethanol withdrawal syndromes. Diverse mechanisms mediate estrogen's protection through neurotrophic, neuroprotective, antiapoptotic, and antioxidant activities. Furthermore, estrogen exerts its neuroprotection through inhibiting inflammation and preserving the homeostasis of neurotransmitters. Estrogen receptors appear to mediate some of estrogen's protection, although it is not yet entirely clear whether it is estrogen receptor- $\alpha$ , estrogen receptor- $\beta$ , or membrane estrogen receptors. At the mitochondrial level, estrogen inhibits peroxidation, eliminates reactive oxygen species, and maintains the homeostasis of mitochondrial membranes/respiration.

The extent to which estrogen can actually ameliorate neurodegenerative diseases in clinical settings may depend on well controlled systematic clinical studies that are largely absent in current situations. Nevertheless, it may be a matter of time that this amazing molecule alleviates the human burden of devastating brain diseases.

## 7. Acknowledgment

This work was supported by National Institute on Alcohol Abuse and Alcoholism (AA015982 and AA018747). We wish to thank Claudia Martinez and David Julovich for their editorial assistance.



## 8. References

- Ajmo, C. T., Jr.; Vernon, D. O.; Collier, L.; Hall, A. A.; Garbuzova-Davis, S.; Willing, A. & Pennypacker, K. R. (2008). The Spleen Contributes to Stroke-Induced Neurodegeneration. *J Neurosci Res*, Vol. 86, No. 10, pp. 2227-34, ISSN 1097-4547
- Amtul, Z.; Wang, L.; Westaway, D. & Rozmahel, R. F. (2010). Neuroprotective Mechanism Conferred by 17beta-Estradiol on the Biochemical Basis of Alzheimer's Disease. *Neuroscience*, Vol. 169, No. 2, pp. 781-6, ISSN 1873-7544
- Andersen, K.; Launer, L. J.; Dewey, M. E.; Letenneur, L.; Ott, A.; Copeland, J. R.; Dartigues, J. F.; Kragh-Sorensen, P.; Baldereschi, M.; Brayne, C.; Lobo, A.; Martinez-Lage, J. M.; Stijnen, T. & Hofman, A. (1999). Gender Differences in the Incidence of Alzheimer's Disease and Vascular Dementia: The Eurodem Studies. Eurodem Incidence Research Group. *Neurology*, Vol. 53, No. 9, pp. 1992-7, ISSN 0028-3878
- Andreassen, O. A.; Ferrante, R. J.; Dedeoglu, A.; Albers, D. W.; Klivenyi, P.; Carlson, E. J.; Epstein, C. J. & Beal, M. F. (2001). Mice with a Partial Deficiency of Manganese Superoxide Dismutase Show Increased Vulnerability to the Mitochondrial Toxins Malonate, 3-Nitropropionic Acid, and MPTP. *Exp Neurol*, Vol. 167, No. 1, pp. 189-95, ISSN 0014-4886
- Arvin, M.; Fedorkova, L.; Disshon, K. A.; Dluzen, D. E. & Leipheimer, R. E. (2000). Estrogen Modulates Responses of Striatal Dopamine Neurons to Mpp(+): Evaluations Using in Vitro and in Vivo Techniques. *Brain Res*, Vol. 872, No. 1-2, pp. 160-71, ISSN 0006-8993
- Association, American Psychiatric. (2000). *Diagnostic and Statistical Manual of Mental Disorders Dsm-Iv-Tr*. 4th ed. (Washington, DC: Amer Psychiatric Pub).
- Azcoitia, I.; Sierra, A.; Veiga, S. & Garcia-Segura, L. M. (2003). Aromatase Expression by Reactive Astroglia Is Neuroprotective. *Ann N Y Acad Sci*, Vol. 1007 pp. 298-305, ISSN 0077-8923
- Azcoitia, I.; Sierra, A.; Veiga, S.; Honda, S.; Harada, N. & Garcia-Segura, L. M. (2001). Brain Aromatase Is Neuroprotective. *J Neurobiol*, Vol. 47, No. 4, pp. 318-29, ISSN 0022-3034
- Barca, O.; Costoya, J. A.; Senaris, R. M. & Arce, V. M. (2008). Interferon-Beta Protects Astrocytes against Tumour Necrosis Factor-Induced Apoptosis Via Activation of P38 Mitogen-Activated Protein Kinase. *Exp Cell Res*, Vol. 314, No. 11-12, pp. 2231-7, ISSN 1090-2422
- Bastide, M.; Ouk, T.; Plaisier, F.; Petrault, O.; Stolc, S. & Bordet, R. (2007). Neurogliovascular Unit after Cerebral Ischemia: Is the Vascular Wall a Pharmacological Target. *Psychoneuroendocrinology*, Vol. 32 Suppl 1 pp. S36-9, ISSN 0306-4530
- Behl, C. & Manthey, D. (2000). Neuroprotective Activities of Estrogen: An Update. *J Neurocytol*, Vol. 29, No. 5-6, pp. 351-8, ISSN 0300-4864
- Benedetti, M. D.; Maraganore, D. M.; Bower, J. H.; McDonnell, S. K.; Peterson, B. J.; Ahlskog, J. E.; Schaid, D. J. & Rocca, W. A. (2001). Hysterectomy, Menopause, and Estrogen Use Preceding Parkinson's Disease: An Exploratory Case-Control Study. *Mov Disord*, Vol. 16, No. 5, pp. 830-7, ISSN 0885-3185
- Beyer, C. & Karolczak, M. (2000). Estrogenic Stimulation of Neurite Growth in Midbrain Dopaminergic Neurons Depends on cAMP/Protein Kinase a Signaling. *J Neurosci Res*, Vol. 59, No. 1, pp. 107-16, ISSN 0360-4012

- Bourque, M.; Dluzen, D. E. & Di Paolo, T. (2009). Neuroprotective Actions of Sex Steroids in Parkinson's Disease. *Front Neuroendocrinol*, Vol. 30, No. 2, pp. 142-57, ISSN 1095-6808
- Brinton, R. D. (2009). Estrogen-Induced Plasticity from Cells to Circuits: Predictions for Cognitive Function. *Trends Pharmacol Sci*, Vol. 30, No. 4, pp. 212-22, ISSN 0165-6147
- Brinton, R. D. (2008). The Healthy Cell Bias of Estrogen Action: Mitochondrial Bioenergetics and Neurological Implications. *Trends Neurosci*, Vol. 31, No. 10, pp. 529-37, ISSN 0166-2236
- Bruce-Keller, A. J.; Dimayuga, F. O.; Reed, J. L.; Wang, C.; Angers, R.; Wilson, M. E.; Dimayuga, V. M. & Scheff, S. W. (2007). Gender and Estrogen Manipulation Do Not Affect Traumatic Brain Injury in Mice. *J Neurotrauma*, Vol. 24, No. 1, pp. 203-15, ISSN 0897-7151
- Burke, W. J. (2003). 3,4-Dihydroxyphenylacetaldehyde: A Potential Target for Neuroprotective Therapy in Parkinson's Disease. *Curr Drug Targets CNS Neurol Disord*, Vol. 2, No. 2, pp. 143-8, ISSN 1568-007X
- Bushnell, C. D. (2008). Stroke and the Female Brain. *Nat Clin Pract Neurol*, Vol. 4, No. 1, pp. 22-33, ISSN 1745-8358
- Carroll, J. C.; Rosario, E. R.; Chang, L.; Stanczyk, F. Z.; Oddo, S.; LaFerla, F. M. & Pike, C. J. (2007). Progesterone and Estrogen Regulate Alzheimer-Like Neuropathology in Female 3xtg-Ad Mice. *J Neurosci*, Vol. 27, No. 48, pp. 13357-65, ISSN 1529-2401
- Chen, H.; Zhang, S. M.; Hernan, M. A.; Schwarzschild, M. A.; Willett, W. C.; Colditz, G. A.; Speizer, F. E. & Ascherio, A. (2003). Nonsteroidal Anti-Inflammatory Drugs and the Risk of Parkinson Disease. *Arch Neurol*, Vol. 60, No. 8, pp. 1059-64, ISSN 0003-9942
- Chen, J. Q. & Yager, J. D. (2004). Estrogen's Effects on Mitochondrial Gene Expression: Mechanisms and Potential Contributions to Estrogen Carcinogenesis. *Ann N Y Acad Sci*, Vol. 1028 pp. 258-72, ISSN 0077-8923
- Coffey, C. E.; Lucke, J. F.; Saxton, J. A.; Ratcliff, G.; Unitas, L. J.; Billig, B. & Bryan, R. N. (1998). Sex Differences in Brain Aging: A Quantitative Magnetic Resonance Imaging Study. *Arch Neurol*, Vol. 55, No. 2, pp. 169-79, ISSN 0003-9942
- Craig, M. C. & Murphy, D. G. (2010). Estrogen Therapy and Alzheimer's Dementia. *Ann N Y Acad Sci*, Vol. 1205 pp. 245-53, ISSN 1749-6632
- Currie, L. J.; Harrison, M. B.; Trugman, J. M.; Bennett, J. P. & Wooten, G. F. (2004). Postmenopausal Estrogen Use Affects Risk for Parkinson Disease. *Arch Neurol*, Vol. 61, No. 6, pp. 886-8, ISSN 0003-9942
- D'Astous, M.; Morissette, M. & Di Paolo, T. (2004). Effect of Estrogen Receptor Agonists Treatment in MPTP Mice: Evidence of Neuroprotection by an ER Alpha Agonist. *Neuropharmacology*, Vol. 47, No. 8, pp. 1180-8, ISSN 0028-3908
- De Butte-Smith, M.; Gulinello, M.; Zukin, R. S. & Etgen, A. M. (2009). Chronic Estradiol Treatment Increases CA1 Cell Survival but Does Not Improve Visual or Spatial Recognition Memory after Global Ischemia in Middle-Aged Female Rats. *Horm Behav*, Vol. 55, No. 3, pp. 442-53, ISSN 1095-6867
- del Zoppo, G. J. & Mabuchi, T. (2003). Cerebral Microvessel Responses to Focal Ischemia. *J Cereb Blood Flow Metab*, Vol. 23, No. 8, pp. 879-94, ISSN 0271-678X
- Dexter, D. T.; Carter, C. J.; Wells, F. R.; Javoy-Agid, F.; Agid, Y.; Lees, A.; Jenner, P. & Marsden, C. D. (1989). Basal Lipid Peroxidation in Substantia Nigra Is Increased in Parkinson's Disease. *J Neurochem*, Vol. 52, No. 2, pp. 381-9, ISSN 0022-3042

- Dhandapani, K. M. & Brann, D. W. (2002). Estrogen-Astrocyte Interactions: Implications for Neuroprotection. *BMC Neurosci*, Vol. 3 pp. 6, ISSN 1471-2202
- Dirnagl, U.; Iadecola, C. & Moskowitz, M. A. (1999). Pathobiology of Ischaemic Stroke: An Integrated View. *Trends Neurosci*, Vol. 22, No. 9, pp. 391-7, ISSN 0166-2236
- Dirnagl, U.; Klehmet, J.; Braun, J. S.; Harms, H.; Meisel, C.; Ziemssen, T.; Prass, K. & Meisel, A. (2007). Stroke-Induced Immunodepression: Experimental Evidence and Clinical Relevance. *Stroke*, Vol. 38, No. 2 Suppl, pp. 770-3, ISSN 1524-4628
- Disshon, K. A.; Boja, J. W. & Dluzen, D. E. (1998). Inhibition of Striatal Dopamine Transporter Activity by 17beta-Estradiol. *Eur J Pharmacol*, Vol. 345, No. 2, pp. 207-11, ISSN 0014-2999
- DonCarlos, L. L.; Azcoitia, I. & Garcia-Segura, L. M. (2009). Neuroprotective Actions of Selective Estrogen Receptor Modulators. *Psychoneuroendocrinology*, Vol. 34 Suppl 1 pp. S113-22, ISSN 1873-3360
- Drechsler, Y.; Dolganiuc, A.; Norkina, O.; Romics, L.; Li, W.; Kodys, K.; Bach, F. H.; Mandrekar, P. & Szabo, G. (2006). Heme Oxygenase-1 Mediates the Anti-Inflammatory Effects of Acute Alcohol on IL-10 Induction Involving P38 MAPK Activation in Monocytes. *J Immunol*, Vol. 177, No. 4, pp. 2592-600, ISSN 0022-1767
- Dubal, D. B.; Zhu, H.; Yu, J.; Rau, S. W.; Shughrue, P. J.; Merchenthaler, I.; Kindy, M. S. & Wise, P. M. (2001). Estrogen Receptor Alpha, Not Beta, Is a Critical Link in Estradiol-Mediated Protection against Brain Injury. *Proc Natl Acad Sci U S A*, Vol. 98, No. 4, pp. 1952-7, ISSN 0027-8424
- Emborg, M. E. (2004). Evaluation of Animal Models of Parkinson's Disease for Neuroprotective Strategies. *J Neurosci Methods*, Vol. 139, No. 2, pp. 121-43, ISSN 0165-0270
- Feigin, V. L. (2005). Stroke Epidemiology in the Developing World. *Lancet*, Vol. 365, No. 9478, pp. 2160-1, ISSN 1474-547X
- Felderhoff-Mueser, U.; Buhrer, C.; Groneck, P.; Obladen, M.; Bartmann, P. & Heep, A. (2003). Soluble Fas (Cd95/Apo-1), Soluble Fas Ligand, and Activated Caspase 3 in the Cerebrospinal Fluid of Infants with Posthemorrhagic and Nonhemorrhagic Hydrocephalus. *Pediatr Res*, Vol. 54, No. 5, pp. 659-64, ISSN 0031-3998
- Felderhoff-Mueser, U.; Taylor, D. L.; Greenwood, K.; Kozma, M.; Stibenz, D.; Joashi, U. C.; Edwards, A. D. & Mehmet, H. (2000). Fas/Cd95/Apo-1 Can Function as a Death Receptor for Neuronal Cells in Vitro and in Vivo and Is Upregulated Following Cerebral Hypoxic-Ischemic Injury to the Developing Rat Brain. *Brain Pathol*, Vol. 10, No. 1, pp. 17-29, ISSN 1015-6305
- Garcia-Segura, L. M. & Balthazart, J. (2009). Steroids and Neuroprotection: New Advances. *Front Neuroendocrinol*, Vol. 30, No. 2, pp. v-ix, ISSN 1095-6808
- Genazzani, A. R.; Pluchino, N.; Luisi, S. & Luisi, M. (2007). Estrogen, Cognition and Female Aging. *Hum Reprod Update*, Vol. 13, No. 2, pp. 175-87, ISSN 1355-4786
- Greenfield, J. P.; Leung, L. W.; Cai, D.; Kaasik, K.; Gross, R. S.; Rodriguez-Boulan, E.; Greengard, P. & Xu, H. (2002). Estrogen Lowers Alzheimer Beta-Amyloid Generation by Stimulating Trans-Golgi Network Vesicle Biogenesis. *J Biol Chem*, Vol. 277, No. 14, pp. 12128-36, ISSN 0021-9258
- Hardy, J. (2004). Toward Alzheimer Therapies Based on Genetic Knowledge. *Annu Rev Med*, Vol. 55 pp. 15-25, ISSN 0066-4219

- Hardy, J. & Selkoe, D. J. (2002). The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. *Science*, Vol. 297, No. 5580, pp. 353-6, ISSN 1095-9203
- Harris, H. A.; Albert, L. M.; Leathurby, Y.; Malamas, M. S.; Mewshaw, R. E.; Miller, C. P.; Kharode, Y. P.; Marzolf, J.; Komm, B. S.; Winneker, R. C.; Frail, D. E.; Henderson, R. A.; Zhu, Y. & Keith, J. C., Jr. (2003). Evaluation of an Estrogen Receptor-Beta Agonist in Animal Models of Human Disease. *Endocrinology*, Vol. 144, No. 10, pp. 4241-9, ISSN 0013-7227
- Hastings, T. G.; Lewis, D. A. & Zigmond, M. J. (1996). Role of Oxidation in the Neurotoxic Effects of Intrastriatal Dopamine Injections. *Proc Natl Acad Sci U S A*, Vol. 93, No. 5, pp. 1956-61, ISSN 0027-8424
- Hawkins, B. T. & Davis, T. P. (2005). The Blood-Brain Barrier/Neurovascular Unit in Health and Disease. *Pharmacol Rev*, Vol. 57, No. 2, pp. 173-85, ISSN 0031-6997
- Hernandez-Munoz, R.; Montiel-Ruiz, C. & Vazquez-Martinez, O. (2000). Gastric Mucosal Cell Proliferation in Ethanol-Induced Chronic Mucosal Injury Is Related to Oxidative Stress and Lipid Peroxidation in Rats. *Lab Invest*, Vol. 80, No. 8, pp. 1161-9, ISSN 0023-6837
- Hunot, S.; Boissiere, F.; Faucheux, B.; Brugg, B.; Mouatt-Prigent, A.; Agid, Y. & Hirsch, E. C. (1996). Nitric Oxide Synthase and Neuronal Vulnerability in Parkinson's Disease. *Neuroscience*, Vol. 72, No. 2, pp. 355-63, ISSN 0306-4522
- Hunot, S. & Hirsch, E. C. (2003). Neuroinflammatory Processes in Parkinson's Disease. *Ann Neurol*, Vol. 53 Suppl 3 pp. S49-58; discussion S58-60, ISSN 0364-5134
- Iivonen, S.; Corder, E.; Lehtovirta, M.; Helisalmi, S.; Mannermaa, A.; Vepsäläinen, S.; Hanninen, T.; Soininen, H. & Hiltunen, M. (2004). Polymorphisms in the CYP19 Gene Confer Increased Risk for Alzheimer Disease. *Neurology*, Vol. 62, No. 7, pp. 1170-6, ISSN 1526-632X
- Ishunina, T. A.; van Beurden, D.; van der Meulen, G.; Unmehopa, U. A.; Hol, E. M.; Huitinga, I. & Swaab, D. F. (2005). Diminished Aromatase Immunoreactivity in the Hypothalamus, but Not in the Basal Forebrain Nuclei in Alzheimer's Disease. *Neurobiol Aging*, Vol. 26, No. 2, pp. 173-94, ISSN 0197-4580
- Ivanova, T.; Kupperts, E.; Engele, J. & Beyer, C. (2001). Estrogen Stimulates Brain-Derived Neurotrophic Factor Expression in Embryonic Mouse Midbrain Neurons through a Membrane-Mediated and Calcium-Dependent Mechanism. *J Neurosci Res*, Vol. 66, No. 2, pp. 221-30, ISSN 0360-4012
- Ivanova, T.; Mendez, P.; Garcia-Segura, L. M. & Beyer, C. (2002). Rapid Stimulation of the PI3K/Akt Signalling Pathway in Developing Midbrain Neurons by Oestrogen. *J Neuroendocrinol*, Vol. 14, No. 1, pp. 73-9, ISSN 0953-8194
- Jaffe, A. B.; Toran-Allerand, C. D.; Greengard, P. & Gandy, S. E. (1994). Estrogen Regulates Metabolism of Alzheimer Amyloid Beta Precursor Protein. *J Biol Chem*, Vol. 269, No. 18, pp. 13065-8, ISSN 0021-9258
- Jia, J.; Guan, D.; Zhu, W.; Alkayed, N. J.; Wang, M. M.; Hua, Z. & Xu, Y. (2009). Estrogen Inhibits Fas-Mediated Apoptosis in Experimental Stroke. *Exp Neurol*, Vol. 215, No. 1, pp. 48-52, ISSN 1090-2430
- Jourdain, S.; Morissette, M.; Morin, N. & Di Paolo, T. (2005). Oestrogens Prevent Loss of Dopamine Transporter (DAT) and Vesicular Monoamine Transporter (VMAT2) in



- Substantia Nigra of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Mice. *J Neuroendocrinol*, Vol. 17, No. 8, pp. 509-17, ISSN 0953-8194
- Jung, M. E.; Agarwal, R. & Simpkins, J. W. (2007). Ethanol Withdrawal Posttranslationally Decreases the Activity of Cytochrome C Oxidase in an Estrogen Reversible Manner. *Neurosci Lett*, Vol. 416, No. 2, pp. 160-4, ISSN 0304-3940
- Jung, M. E.; Ju, X.; Metzger, D. B. & Simpkins, J. W. (2011). Ethanol Withdrawal Hastens the Aging of Cytochrome C Oxidase. *Neurobiol Aging*, pp. 1558-1497, ISSN 1558-1497
- Jung, M. E.; Ju, X.; Simpkins, J. W.; Metzger, D. B.; Yan, L. J. & Wen, Y. (2010). Ethanol Withdrawal Acts as an Age-Specific Stressor to Activate Cerebellar P38 Kinase. *Neurobiol Aging* pp. 1558-1497, ISSN 1558-1497
- Jung, M. E. & Metzger, D. B. (2010). Alcohol Withdrawal and Brain Injuries: Beyond Classical Mechanisms. *Molecules*, Vol. 15, No. 7, pp. 4984-5011, ISSN 1420-3049
- Jung, M. E.; Rewal, M.; Perez, E.; Wen, Y. & Simpkins, J. W. (2004). Estrogen Protects against Brain Lipid Peroxidation in Ethanol-Withdrawn Rats. *Pharmacol Biochem Behav*, Vol. 79, No. 3, pp. 573-86, ISSN 0091-3057
- Jung, M. E.; Wilson, A. M.; Ju, X.; Wen, Y.; Metzger, D. B. & Simpkins, J. W. (2009). Ethanol Withdrawal Provokes Opening of the Mitochondrial Membrane Permeability Transition Pore in an Estrogen-Preventable Manner. *J Pharmacol Exp Ther*, Vol. 328, No. 3, pp. 692-8, ISSN 1521-0103
- Jung, M. E.; Wilson, A. M. & Simpkins, J. W. (2006). A Nonfeminizing Estrogen Analog Protects against Ethanol Withdrawal Toxicity in Immortalized Hippocampal Cells. *J Pharmacol Exp Ther*, Vol. 319, No. 2, pp. 543-50, ISSN 0022-3565
- Karakaya, S.; Kipp, M. & Beyer, C. (2007). Oestrogen Regulates the Expression and Function of Dopamine Transporters in Astrocytes of the Nigrostriatal System. *J Neuroendocrinol*, Vol. 19, No. 9, pp. 682-90, ISSN 0953-8194
- Knott, C.; Stern, G. & Wilkin, G. P. (2000). Inflammatory Regulators in Parkinson's Disease: iNOS, Lipocortin-1, and Cyclooxygenases-1 and -2. *Mol Cell Neurosci*, Vol. 16, No. 6, pp. 724-39, ISSN 1044-7431
- Ku, B. M.; Lee, Y. K.; Jeong, J. Y.; Mun, J.; Han, J. Y.; Roh, G. S.; Kim, H. J.; Cho, G. J.; Choi, W. S.; Yi, G. S. & Kang, S. S. (2007). Ethanol-Induced Oxidative Stress Is Mediated by P38 MAPK Pathway in Mouse Hippocampal Cells. *Neurosci Lett*, Vol. 419, No. 1, pp. 64-7, ISSN 0304-3940
- Lang, A. E. (2007). The Progression of Parkinson Disease: A Hypothesis. *Neurology*, Vol. 68, No. 12, pp. 948-52, ISSN 1526-632X
- Lebesgue, D.; Chevalleyre, V.; Zukin, R. S. & Etgen, A. M. (2009). Estradiol Rescues Neurons from Global Ischemia-Induced Cell Death: Multiple Cellular Pathways of Neuroprotection. *Steroids*, Vol. 74, No. 7, pp. 555-61, ISSN 0039-128X
- LeBlanc, E. S.; Janowsky, J.; Chan, B. K. & Nelson, H. D. (2001). Hormone Replacement Therapy and Cognition: Systematic Review and Meta-Analysis. *JAMA*, Vol. 285, No. 11, pp. 1489-99, ISSN 0098-7484
- Li, J.; Siegel, M.; Yuan, M.; Zeng, Z.; Finnucan, L.; Persky, R.; Hurn, P. D. & McCullough, L. D. (2011). Estrogen Enhances Neurogenesis and Behavioral Recovery after Stroke. *J Cereb Blood Flow Metab*, Vol. 31, No. 2, pp. 413-25, ISSN 1559-7016
- Li, R.; Shen, Y.; Yang, L. B.; Lue, L. F.; Finch, C. & Rogers, J. (2000). Estrogen Enhances Uptake of Amyloid Beta-Protein by Microglia Derived from the Human Cortex. *J Neurochem*, Vol. 75, No. 4, pp. 1447-54, ISSN 0022-3042



- Liang, K.; Yang, L.; Yin, C.; Xiao, Z.; Zhang, J.; Liu, Y. & Huang, J. (2010). Estrogen Stimulates Degradation of Beta-Amyloid Peptide by up-Regulating Neprilysin. *J Biol Chem*, Vol. 285, No. 2, pp. 935-42, ISSN 1083-351X
- Liu, B. & Dluzen, D. E. (2006). Effect of Estrogen Upon Methamphetamine-Induced Neurotoxicity within the Impaired Nigrostriatal Dopaminergic System. *Synapse*, Vol. 60, No. 5, pp. 354-61, ISSN 0887-4476
- Liu, B. & Hong, J. S. (2003). Role of Microglia in Inflammation-Mediated Neurodegenerative Diseases: Mechanisms and Strategies for Therapeutic Intervention. *J Pharmacol Exp Ther*, Vol. 304, No. 1, pp. 1-7, ISSN 0022-3565
- Liu, F.; Day, M.; Muniz, L. C.; Bitran, D.; Arias, R.; Revilla-Sanchez, R.; Grauer, S.; Zhang, G.; Kelley, C.; Pulito, V.; Sung, A.; Mervis, R. F.; Navarra, R.; Hirst, W. D.; Reinhart, P. H.; Marquis, K. L.; Moss, S. J.; Pangalos, M. N. & Brandon, N. J. (2008). Activation of Estrogen Receptor-Beta Regulates Hippocampal Synaptic Plasticity and Improves Memory. *Nat Neurosci*, Vol. 11, No. 3, pp. 334-43, ISSN 1097-6256
- Liu, L.; Kim, J. Y.; Koike, M. A.; Yoon, Y. J.; Tang, X. N.; Ma, H.; Lee, H.; Steinberg, G. K.; Lee, J. E. & Yenari, M. A. (2008). FasL Shedding Is Reduced by Hypothermia in Experimental Stroke. *J Neurochem*, Vol. 106, No. 2, pp. 541-50, ISSN 1471-4159
- Liu, R.; Wen, Y.; Perez, E.; Wang, X.; Day, A. L.; Simpkins, J. W. & Yang, S. H. (2005). 17beta-Estradiol Attenuates Blood-Brain Barrier Disruption Induced by Cerebral Ischemia-Reperfusion Injury in Female Rats. *Brain Res*, Vol. 1060, No. 1-2, pp. 55-61, ISSN 0006-8993
- Logan, S. M.; Sarkar, S. N.; Zhang, Z. & Simpkins, J. W. (2011). Estrogen-Induced Signaling Attenuates Soluble A $\beta$  Peptide-Mediated Dysfunction of Pathways in Synaptic Plasticity. *Brain Res*, Vol. 1383 pp. 1-12, ISSN 1872-6240
- Luchetti, S.; Huitinga, I. & Swaab, D. F. (2011). Neurosteroid and GABA-a Receptor Alterations in Alzheimer's Disease, Parkinson's Disease and Multiple Sclerosis. *Neuroscience* pp. 1873-7544, ISSN 1873-7544
- Luo, Y.; Umegaki, H.; Wang, X.; Abe, R. & Roth, G. S. (1998). Dopamine Induces Apoptosis through an Oxidation-Involved SAPK/JNK Activation Pathway. *J Biol Chem*, Vol. 273, No. 6, pp. 3756-64, ISSN 0021-9258
- Luth, H. J.; Holzer, M.; Gartner, U.; Staufenbiel, M. & Arendt, T. (2001). Expression of Endothelial and Inducible NOS-isoforms Is Increased in Alzheimer's Disease, in APP23 Transgenic Mice and after Experimental Brain Lesion in Rat: Evidence for an Induction by Amyloid Pathology. *Brain Res*, Vol. 913, No. 1, pp. 57-67, ISSN 0006-8993
- Maggi, A.; Ciana, P.; Belcredito, S. & Vegeto, E. (2004). Estrogens in the Nervous System: Mechanisms and Nonreproductive Functions. *Annu Rev Physiol*, Vol. 66 pp. 291-313, ISSN 0066-4278
- Marotta, F.; Reizakovic, I.; Tajiri, H.; Safran, P. & Ideo, G. (1997). Abstinence-Induced Oxidative Stress in Moderate Drinkers Is Improved by Bionormalizer. *Hepatogastroenterology*, Vol. 44, No. 17, pp. 1360-6, ISSN 0172-6390
- Marrian, G. F. & Butenandt, A. (1931). Oestrus-Producing Hormones. *Science*, Vol. 74, No. 1926, pp. 547, ISSN 0036-8075
- Mattson, M. P.; Culmsee, C. & Yu, Z. F. (2000). Apoptotic and Antiapoptotic Mechanisms in Stroke. *Cell Tissue Res*, Vol. 301, No. 1, pp. 173-87, ISSN 0302-766X

- McGeer, P. L.; Itagaki, S.; Boyes, B. E. & McGeer, E. G. (1988). Reactive Microglia Are Positive for HLA-DR in the Substantia Nigra of Parkinson's and Alzheimer's Disease Brains. *Neurology*, Vol. 38, No. 8, pp. 1285-91, ISSN 0028-3878
- McGeer, P. L.; Rogers, J. & McGeer, E. G. (2006). Inflammation, Anti-Inflammatory Agents and Alzheimer Disease: The Last 12 Years. *J Alzheimers Dis*, Vol. 9, No. 3 Suppl, pp. 271-6, ISSN 1387-2877
- Meisel, C.; Schwab, J. M.; Prass, K.; Meisel, A. & Dirnagl, U. (2005). Central Nervous System Injury-Induced Immune Deficiency Syndrome. *Nat Rev Neurosci*, Vol. 6, No. 10, pp. 775-86, ISSN 1471-003X
- Miller, N. R.; Jover, T.; Cohen, H. W.; Zukin, R. S. & Etgen, A. M. (2005). Estrogen Can Act Via Estrogen Receptor Alpha and Beta to Protect Hippocampal Neurons against Global Ischemia-Induced Cell Death. *Endocrinology*, Vol. 146, No. 7, pp. 3070-9, ISSN 0013-7227
- Montoliu, C.; Valles, S.; Renau-Piqueras, J. & Guerri, C. (1994). Ethanol-Induced Oxygen Radical Formation and Lipid Peroxidation in Rat Brain: Effect of Chronic Alcohol Consumption. *J Neurochem*, Vol. 63, No. 5, pp. 1855-62, ISSN 0022-3042
- Morale, M. C.; Serra, P. A.; L'Episcopo, F.; Tirolo, C.; Caniglia, S.; Testa, N.; Gennuso, F.; Giaquinta, G.; Rocchitta, G.; Desole, M. S.; Miele, E. & Marchetti, B. (2006). Estrogen, Neuroinflammation and Neuroprotection in Parkinson's Disease: Glia Dictates Resistance Versus Vulnerability to Neurodegeneration. *Neuroscience*, Vol. 138, No. 3, pp. 869-78, ISSN 0306-4522
- Moriguchi, T.; Toyoshima, F.; Gotoh, Y.; Iwamatsu, A.; Irie, K.; Mori, E.; Kuroyanagi, N.; Hagiwara, M.; Matsumoto, K. & Nishida, E. (1996). Purification and Identification of a Major Activator for P38 from Osmotically Shocked Cells. Activation of Mitogen-Activated Protein Kinase Kinase 6 by Osmotic Shock, Tumor Necrosis Factor-Alpha, and H<sub>2</sub>O<sub>2</sub>. *J Biol Chem*, Vol. 271, No. 43, pp. 26981-8, ISSN 0021-9258
- Morinaga, A.; Hirohata, M.; Ono, K. & Yamada, M. (2007). Estrogen Has Anti-Amyloidogenic Effects on Alzheimer's Beta-Amyloid Fibrils *in vitro*. *Biochem Biophys Res Commun*, Vol. 359, No. 3, pp. 697-702, ISSN 0006-291X
- Nalivaeva, N. N.; Fisk, L. R.; Belyaev, N. D. & Turner, A. J. (2008). Amyloid-Degrading Enzymes as Therapeutic Targets in Alzheimer's Disease. *Curr Alzheimer Res*, Vol. 5, No. 2, pp. 212-24, ISSN 1567-2050
- Niewada, M.; Kobayashi, A.; Sandercock, P. A.; Kaminski, B. & Czlonkowska, A. (2005). Influence of Gender on Baseline Features and Clinical Outcomes among 17,370 Patients with Confirmed Ischemic Stroke in the International Stroke Trial. *Neuroepidemiology*, Vol. 24, No. 3, pp. 123-8, ISSN 0251-5350
- Nordmann, R.; Ribiere, C. & Rouach, H. (1990). Ethanol-Induced Lipid Peroxidation and Oxidative Stress in Extrahepatic Tissues. *Alcohol Alcohol*, Vol. 25, No. 2-3, pp. 231-7, ISSN 0735-0414
- Norkina, O.; Dolganiuc, A.; Shapiro, T.; Kodys, K.; Mandrekar, P. & Szabo, G. (2007). Acute Alcohol Activates STAT3, AP-1, and SP-1 Transcription Factors Via the Family of Src Kinases to Promote IL-10 Production in Human Monocytes. *J Leukoc Biol*, Vol. 82, No. 3, pp. 752-62, ISSN 0741-5400
- Offner, H.; Vandenbark, A. A. & Hurn, P. D. (2009). Effect of Experimental Stroke on Peripheral Immunity: CNS Ischemia Induces Profound Immunosuppression. *Neuroscience*, Vol. 158, No. 3, pp. 1098-111, ISSN 0306-4522

- Oldendorf, W. H.; Cornford, M. E. & Brown, W. J. (1977). The Large Apparent Work Capability of the Blood-Brain Barrier: A Study of the Mitochondrial Content of Capillary Endothelial Cells in Brain and Other Tissues of the Rat. *Ann Neurol*, Vol. 1, No. 5, pp. 409-17, ISSN 0364-5134
- Park, E. M.; Cho, S.; Frys, K. A.; Glickstein, S. B.; Zhou, P.; Anrather, J.; Ross, M. E. & Iadecola, C. (2006). Inducible Nitric Oxide Synthase Contributes to Gender Differences in Ischemic Brain Injury. *J Cereb Blood Flow Metab*, Vol. 26, No. 3, pp. 392-401, ISSN 0271-678X
- Pelligrino, D. A.; Santizo, R.; Baughman, V. L. & Wang, Q. (1998). Cerebral Vasodilating Capacity During Forebrain Ischemia: Effects of Chronic Estrogen Depletion and Repletion and the Role of Neuronal Nitric Oxide Synthase. *Neuroreport*, Vol. 9, No. 14, pp. 3285-91, ISSN 0959-4965
- Peters, O.; Back, T.; Lindauer, U.; Busch, C.; Megow, D.; Dreier, J. & Dirnagl, U. (1998). Increased Formation of Reactive Oxygen Species after Permanent and Reversible Middle Cerebral Artery Occlusion in the Rat. *J Cereb Blood Flow Metab*, Vol. 18, No. 2, pp. 196-205, ISSN 0271-678X
- Petito, C. K.; Kraig, R. P. & Pulsinelli, W. A. (1987). Light and Electron Microscopic Evaluation of Hydrogen Ion-Induced Brain Necrosis. *J Cereb Blood Flow Metab*, Vol. 7, No. 5, pp. 625-32, ISSN 0271-678X
- Pfeilschifter, J.; Koditz, R.; Pfohl, M. & Schatz, H. (2002). Changes in Proinflammatory Cytokine Activity after Menopause. *Endocr Rev*, Vol. 23, No. 1, pp. 90-119, ISSN 0163-769X
- Polanczyk, M.; Zamora, A.; Subramanian, S.; Matejuk, A.; Hess, D. L.; Blankenhorn, E. P.; Teuscher, C.; Vandenbark, A. A. & Offner, H. (2003). The Protective Effect of 17beta-Estradiol on Experimental Autoimmune Encephalomyelitis Is Mediated through Estrogen Receptor-Alpha. *Am J Pathol*, Vol. 163, No. 4, pp. 1599-605, ISSN 0002-9440
- Pozzilli, C.; Falaschi, P.; Mainero, C.; Martocchia, A.; D'Urso, R.; Proietti, A.; Frontoni, M.; Bastianello, S. & Filippi, M. (1999). MRI in Multiple Sclerosis During the Menstrual Cycle: Relationship with Sex Hormone Patterns. *Neurology*, Vol. 53, No. 3, pp. 622-4, ISSN 0028-3878
- Prokai-Tatrai, K.; Perjesi, P.; Rivera-Portalatin, N. M.; Simpkins, J. W. & Prokai, L. (2008). Mechanistic Investigations on the Antioxidant Action of a Neuroprotective Estrogen Derivative. *Steroids*, Vol. 73, No. 3, pp. 280-8, ISSN 0039-128X
- Prokai, L.; Prokai-Tatrai, K.; Perjesi, P.; Zharikova, A. D.; Perez, E. J.; Liu, R. & Simpkins, J. W. (2003). Quinol-Based Cyclic Antioxidant Mechanism in Estrogen Neuroprotection. *Proc Natl Acad Sci U S A*, Vol. 100, No. 20, pp. 11741-6, ISSN 0027-8424
- Przedborski, S.; Kostic, V.; Jackson-Lewis, V.; Naini, A. B.; Simonetti, S.; Fahn, S.; Carlson, E.; Epstein, C. J. & Cadet, J. L. (1992). Transgenic Mice with Increased Cu/Zn-Superoxide Dismutase Activity Are Resistant to N-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Neurotoxicity. *J Neurosci*, Vol. 12, No. 5, pp. 1658-67, ISSN 0270-6474
- Ragonese, P.; D'Amelio, M.; Salemi, G.; Aridon, P.; Gammino, M.; Epifanio, A.; Morgante, L. & Savettieri, G. (2004). Risk of Parkinson Disease in Women: Effect of Reproductive Characteristics. *Neurology*, Vol. 62, No. 11, pp. 2010-4, ISSN 1526-632X

- Rewal, M.; Wen, Y.; Wilson, A.; Simpkins, J. W. & Jung, M. E. (2005). Role of Parvalbumin in Estrogen Protection from Ethanol Withdrawal Syndrome. *Alcohol Clin Exp Res*, Vol. 29, No. 10, pp. 1837-44, ISSN 0145-6008
- Rosario, E. R.; Chang, L.; Head, E. H.; Stanczyk, F. Z. & Pike, C. J. (2011). Brain Levels of Sex Steroid Hormones in Men and Women During Normal Aging and in Alzheimer's Disease. *Neurobiol Aging*, Vol. 32, No. 4, pp. 604-13, ISSN 1558-1497
- Rosenbaum, D. M.; Gupta, G.; D'Amore, J.; Singh, M.; Weidenheim, K.; Zhang, H. & Kessler, J. A. (2000). Fas (CD95/APO-1) Plays a Role in the Pathophysiology of Focal Cerebral Ischemia. *J Neurosci Res*, Vol. 61, No. 6, pp. 686-92, ISSN 0360-4012
- Rossetti, Z. L. & Carboni, S. (1995). Ethanol Withdrawal Is Associated with Increased Extracellular Glutamate in the Rat Striatum. *Eur J Pharmacol*, Vol. 283, No. 1-3, pp. 177-83, ISSN 0014-2999
- Saido, T. C. (1998). Alzheimer's Disease as Proteolytic Disorders: Anabolism and Catabolism of Beta-Amyloid. *Neurobiol Aging*, Vol. 19, No. 1 Suppl, pp. S69-75, ISSN 0197-4580
- Sano, M.; Jacobs, D.; Andrews, H.; Bell, K.; Graff-Radford, N.; Lucas, J.; Rabins, P.; Bolla, K.; Tsai, W. Y.; Cross, P.; Andrews, K.; Costa, R. & Xiaodong, Luo. (2008). A Multi-Center, Randomized, Double Blind Placebo-Controlled Trial of Estrogens to Prevent Alzheimer's Disease and Loss of Memory in Women: Design and Baseline Characteristics. *Clin Trials*, Vol. 5, No. 5, pp. 523-33, ISSN 1740-7745
- Saunders-Pullman, R.; Derby, C.; Santoro, N.; Bressman, S.; Chiu, R.B.; Lipton, R.B.; Wassertheil-Smoller, S. (2009). Role of Endogenous and Exogenous Hormone Exposure on the Risk of Parkinson Disease: Results from the Women's Health Initiative Observational Study. *American Academy of Neurology*
- Selkoe, D. J. (2000). The Genetics and Molecular Pathology of Alzheimer's Disease: Roles of Amyloid and the Presenilins. *Neurol Clin*, Vol. 18, No. 4, pp. 903-22, ISSN 0733-8619
- Selvamani, A. & Sohrabji, F. (2010). Reproductive Age Modulates the Impact of Focal Ischemia on the Forebrain as Well as the Effects of Estrogen Treatment in Female Rats. *Neurobiol Aging*, Vol. 31, No. 9, pp. 1618-28, ISSN 1558-1497
- Sherwin, B. B. (2007). The Clinical Relevance of the Relationship between Estrogen and Cognition in Women. *J Steroid Biochem Mol Biol*, Vol. 106, No. 1-5, pp. 151-6, ISSN 0960-0760
- Sherwin, B. B. (2009). Estrogen Therapy: Is Time of Initiation Critical for Neuroprotection? *Nat Rev Endocrinol*, Vol. 5, No. 11, pp. 620-7, ISSN 1759-5037
- Sherwin, B.B.; Chertkow, H.; Schipper, H.; Nasreddine, Z. (2011). A Randomized Controlled Trial of Estrogen Treatment in Men with Mild Cognitive Impairment. *Neurobiol Aging*
- Shughrue, P. J. (2004). Estrogen Attenuates the MPTP-Induced Loss of Dopamine Neurons from the Mouse SNC Despite a Lack of Estrogen Receptors (Eralpha and Erbeta). *Exp Neurol*, Vol. 190, No. 2, pp. 468-77, ISSN 0014-4886
- Shulman, L. M. & Bhat, V. (2006). Gender Disparities in Parkinson's Disease. *Expert Rev Neurother*, Vol. 6, No. 3, pp. 407-16, ISSN 1744-8360
- Sian, J.; Dexter, D. T.; Lees, A. J.; Daniel, S.; Agid, Y.; Javoy-Agid, F.; Jenner, P. & Marsden, C. D. (1994). Alterations in Glutathione Levels in Parkinson's Disease and Other Neurodegenerative Disorders Affecting Basal Ganglia. *Ann Neurol*, Vol. 36, No. 3, pp. 348-55, ISSN 0364-5134



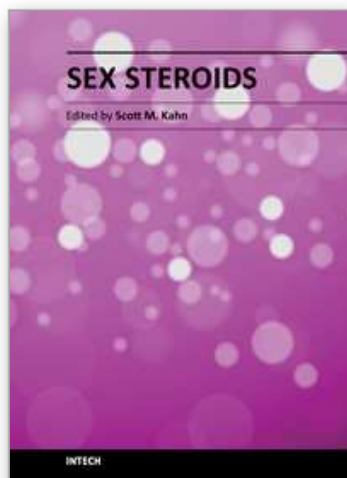
- Simpkins, J. W.; Singh, M. & Bishop, J. (1994). The Potential Role for Estrogen Replacement Therapy in the Treatment of the Cognitive Decline and Neurodegeneration Associated with Alzheimer's Disease. *Neurobiol Aging*, Vol. 15 Suppl 2 pp. S195-7, ISSN 0197-4580
- Smith, M. A.; Richey Harris, P. L.; Sayre, L. M.; Beckman, J. S. & Perry, G. (1997). Widespread Peroxynitrite-Mediated Damage in Alzheimer's Disease. *J Neurosci*, Vol. 17, No. 8, pp. 2653-7, ISSN 0270-6474
- St George-Hyslop, P. H. (2000). Genetic Factors in the Genesis of Alzheimer's Disease. *Ann N Y Acad Sci*, Vol. 924 pp. 1-7, ISSN 0077-8923
- Sugawara, T.; Kinouchi, H.; Oda, M.; Shoji, H.; Omae, T. & Mizoi, K. (2005). Candesartan Reduces Superoxide Production after Global Cerebral Ischemia. *Neuroreport*, Vol. 16, No. 4, pp. 325-8, ISSN 0959-4965
- Suzuki, S.; Brown, C. M. & Wise, P. M. (2009). Neuroprotective Effects of Estrogens Following Ischemic Stroke. *Front Neuroendocrinol*, Vol. 30, No. 2, pp. 201-11, ISSN 1095-6808
- Szego, E. M.; Csorba, A.; Janaky, T.; Kekesi, K. A.; Abraham, I. M.; Morotz, G. M.; Penke, B.; Palkovits, M.; Murvai, U.; Kellermayer, M. S.; Kardos, J. & Juhasz, G. D. (2011). Effects of Estrogen on Beta-Amyloid-Induced Cholinergic Cell Death in the Nucleus Basalis Magnocellularis. *Neuroendocrinology*, Vol. 93, No. 2, pp. 90-105, ISSN 1423-0194
- Tanzi, R. E. & Bertram, L. (2005). Twenty Years of the Alzheimer's Disease Amyloid Hypothesis: A Genetic Perspective. *Cell*, Vol. 120, No. 4, pp. 545-55, ISSN 0092-8674
- Towfighi, A.; Saver, J. L.; Engelhardt, R. & Ovbiagele, B. (2007). A Midlife Stroke Surge among Women in the United States. *Neurology*, Vol. 69, No. 20, pp. 1898-904, ISSN 1526-632X
- Tripanichkul, W.; Sripanichkulchai, K.; Duce, J. A. & Finkelstein, D. I. (2007). 17beta-Estradiol Reduces Nitrotyrosine Immunoreactivity and Increases SOD1 and SOD2 Immunoreactivity in Nigral Neurons in Male Mice Following MPTP Insult. *Brain Res*, Vol. 1164 pp. 24-31, ISSN 0006-8993
- Tsai, G. E.; Ragan, P.; Chang, R.; Chen, S.; Linnoila, V. M. & Coyle, J. T. (1998). Increased Glutamatergic Neurotransmission and Oxidative Stress after Alcohol Withdrawal. *Am J Psychiatry*, Vol. 155, No. 6, pp. 726-32, ISSN 0002-953X
- Valles, S. L.; Dolz-Gaiton, P.; Gambini, J.; Borrás, C.; Lloret, A.; Pallardo, F. V. & Vina, J. (2010). Estradiol or Genistein Prevent Alzheimer's Disease-Associated Inflammation Correlating with an Increase PPAR Gamma Expression in Cultured Astrocytes. *Brain Res*, Vol. 1312 pp. 138-44, ISSN 1872-6240
- Vallett, M.; Tabatabaie, T.; Briscoe, R. J.; Baird, T. J.; Beatty, W. W.; Floyd, R. A. & Gauvin, D. V. (1997). Free Radical Production During Ethanol Intoxication, Dependence, and Withdrawal. *Alcohol Clin Exp Res*, Vol. 21, No. 2, pp. 275-85, ISSN 0145-6008
- Vegeto, E.; Belcredito, S.; Etteri, S.; Ghisletti, S.; Brusadelli, A.; Meda, C.; Krust, A.; Dupont, S.; Ciana, P.; Chambon, P. & Maggi, A. (2003). Estrogen Receptor-Alpha Mediates the Brain Antiinflammatory Activity of Estradiol. *Proc Natl Acad Sci U S A*, Vol. 100, No. 16, pp. 9614-9, ISSN 0027-8424
- Vegeto, E.; Belcredito, S.; Ghisletti, S.; Meda, C.; Etteri, S. & Maggi, A. (2006). The Endogenous Estrogen Status Regulates Microglia Reactivity in Animal Models of Neuroinflammation. *Endocrinology*, Vol. 147, No. 5, pp. 2263-72, ISSN 0013-7227



- Vegeto, E.; Benedusi, V. & Maggi, A. (2008). Estrogen Anti-Inflammatory Activity in Brain: A Therapeutic Opportunity for Menopause and Neurodegenerative Diseases. *Front Neuroendocrinol*, Vol. 29, No. 4, pp. 507-19, ISSN 1095-6808
- Vegeto, E.; Bonincontro, C.; Pollio, G.; Sala, A.; Viappiani, S.; Nardi, F.; Brusadelli, A.; Viviani, B.; Ciana, P. & Maggi, A. (2001). Estrogen Prevents the Lipopolysaccharide-Induced Inflammatory Response in Microglia. *J Neurosci*, Vol. 21, No. 6, pp. 1809-18, ISSN 1529-2401
- Viscoli, C. M.; Brass, L. M.; Kernan, W. N.; Sarrel, P. M.; Suissa, S. & Horwitz, R. I. (2001). A Clinical Trial of Estrogen-Replacement Therapy after Ischemic Stroke. *N Engl J Med*, Vol. 345, No. 17, pp. 1243-9, ISSN 0028-4793
- Wahner, A. D.; Bronstein, J. M.; Bordelon, Y. M. & Ritz, B. (2007). Nonsteroidal Anti-Inflammatory Drugs May Protect against Parkinson's Disease. *Neurology*, Vol. 69, No. 19, pp. 1836-42, ISSN 1526-632X
- Wang, X.; Ellison, J. A.; Siren, A. L.; Lysko, P. G.; Yue, T. L.; Barone, F. C.; Shatzman, A. & Feuerstein, G. Z. (1998). Prolonged Expression of Interferon-Inducible Protein-10 in Ischemic Cortex after Permanent Occlusion of the Middle Cerebral Artery in Rat. *J Neurochem*, Vol. 71, No. 3, pp. 1194-204, ISSN 0022-3042
- Wang, X.; Yue, T. L.; Barone, F. C.; White, R. F.; Gagnon, R. C. & Feuerstein, G. Z. (1994). Concomitant Cortical Expression of TNF-alpha and IL-1 beta mRNAs Follows Early Response Gene Expression in Transient Focal Ischemia. *Mol Chem Neuropathol*, Vol. 23, No. 2-3, pp. 103-14, ISSN 1044-7393
- Wang, X.; Yue, T. L.; Young, P. R.; Barone, F. C. & Feuerstein, G. Z. (1995). Expression of Interleukin-6, C-Fos, and Zif268 mRNAs in Rat Ischemic Cortex. *J Cereb Blood Flow Metab*, Vol. 15, No. 1, pp. 166-71, ISSN 0271-678X
- Wassertheil-Smoller, S.; Hendrix, S. L.; Limacher, M.; Heiss, G.; Kooperberg, C.; Baird, A.; Kotchen, T.; Curb, J. D.; Black, H.; Rossouw, J. E.; Aragaki, A.; Safford, M.; Stein, E.; Laowattana, S. & Mysiw, W. J. (2003). Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women: The Women's Health Initiative: A Randomized Trial. *JAMA*, Vol. 289, No. 20, pp. 2673-84, ISSN 0098-7484
- Weill-Engerer, S.; David, J. P.; Sazdovitch, V.; Liere, P.; Eychenne, B.; Pianos, A.; Schumacher, M.; Delacourte, A.; Baulieu, E. E. & Akwa, Y. (2002). Neurosteroid Quantification in Human Brain Regions: Comparison between Alzheimer's and Nondemented Patients. *J Clin Endocrinol Metab*, Vol. 87, No. 11, pp. 5138-43, ISSN 0021-972X
- Wober, C.; Wober-Bingol, C.; Karwautz, A.; Nimmerrichter, A.; Walter, H. & Deecke, L. (1998). Ataxia of Stance in Different Types of Alcohol Dependence--a Posturographic Study. *Alcohol Alcohol*, Vol. 33, No. 4, pp. 393-402, ISSN 0735-0414
- Xu, H.; Gouras, G. K.; Greenfield, J. P.; Vincent, B.; Naslund, J.; Mazzarelli, L.; Fried, G.; Jovanovic, J. N.; Seeger, M.; Relkin, N. R.; Liao, F.; Checler, F.; Buxbaum, J. D.; Chait, B. T.; Thinakaran, G.; Sisodia, S. S.; Wang, R.; Greengard, P. & Gandy, S. (1998). Estrogen Reduces Neuronal Generation of Alzheimer Beta-Amyloid Peptides. *Nat Med*, Vol. 4, No. 4, pp. 447-51, ISSN 1078-8956
- Yamin, G.; Ono, K.; Inayathullah, M. & Teplow, D. B. (2008). Amyloid Beta-Protein Assembly as a Therapeutic Target of Alzheimer's Disease. *Curr Pharm Des*, Vol. 14, No. 30, pp. 3231-46, ISSN 1873-4286

- Yue, X.; Lu, M.; Lancaster, T.; Cao, P.; Honda, S.; Staufenbiel, M.; Harada, N.; Zhong, Z.; Shen, Y. & Li, R. (2005). Brain Estrogen Deficiency Accelerates A $\beta$  Plaque Formation in an Alzheimer's Disease Animal Model. *Proc Natl Acad Sci U S A*, Vol. 102, No. 52, pp. 19198-203, ISSN 0027-8424
- Zandi, P. P.; Carlson, M. C.; Plassman, B. L.; Welsh-Bohmer, K. A.; Mayer, L. S.; Steffens, D. C. & Breitner, J. C. (2002). Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women: The Cache County Study. *JAMA*, Vol. 288, No. 17, pp. 2123-9, ISSN 0098-7484
- Zhang, B.; Subramanian, S.; Dziennis, S.; Jia, J.; Uchida, M.; Akiyoshi, K.; Migliati, E.; Lewis, A. D.; Vandenbark, A. A.; Offner, H. & Hurn, P. D. (2010). Estradiol and G1 Reduce Infarct Size and Improve Immunosuppression after Experimental Stroke. *J Immunol*, Vol. 184, No. 8, pp. 4087-94, ISSN 1550-6606
- Zhang, J.; Graham, D. G.; Montine, T. J. & Ho, Y. S. (2000). Enhanced N-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Toxicity in Mice Deficient in Cu Zn-Superoxide Dismutase or Glutathione Peroxidase. *J Neuropathol Exp Neurol*, Vol. 59, No. 1, pp. 53-61, ISSN 0022-3069
- Zhang, Q. G.; Raz, L.; Wang, R.; Han, D.; De Sevilla, L.; Yang, F.; Vadlamudi, R. K. & Brann, D. W. (2009). Estrogen Attenuates Ischemic Oxidative Damage Via an Estrogen Receptor Alpha-Mediated Inhibition of NADPH Oxidase Activation. *J Neurosci*, Vol. 29, No. 44, pp. 13823-36, ISSN 1529-2401
- Zheng, H.; Xu, H.; Uljon, S.N.; Gross, R.; Hardy, K.; Gaynor, J.; Lafrancois, J.; Simpkins, J.; Refolo, L.M.; Petanceska, S.; Wang, R.; Duff, K. (2002). Modulation of A $\beta$  Peptides by Estrogen in Mouse Models. *J Neurochem*, Vol. 80, No. 1, pp. 191-6, ISSN
- Zhu, X.; Su, B.; Wang, X.; Smith, M. A. & Perry, G. (2007). Causes of Oxidative Stress in Alzheimer Disease. *Cell Mol Life Sci*, Vol. 64, No. 17, pp. 2202-10, ISSN 1420-682X

IntechOpen



## **Sex Steroids**

Edited by Dr. Scott M. Kahn

ISBN 978-953-307-857-1

Hard cover, 330 pages

**Publisher** InTech

**Published online** 27, January, 2012

**Published in print edition** January, 2012

This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Xiaohua Ju, Daniel Metzger and Marianna Jung (2012). Estrogen and Brain Protection, Sex Steroids, Dr. Scott M. Kahn (Ed.), ISBN: 978-953-307-857-1, InTech, Available from: <http://www.intechopen.com/books/sex-steroids/estrogen-and-brain-protection>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen